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Short communication

Pharmacodynamics of propofol and alfaxalone in rattlesnakes (*Crotalus durissus*)

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ABSTRACT

To characterise the effect of two common induction agents, propofol and alfaxalone, on mean arterial blood pressure (MAP) and heart rate (HR), we equipped 19 adult South American rattlesnakes (*Crotalus durissus*) with an indwelling arterial catheter approximately 24 h prior to recording of baseline resting values. Then, seven snakes received alfaxalone (15 mg kg^{-1}) intravascularly (IV) through the catheter, while groups two and three (both $n = 6$) received propofol (15 mg kg^{-1} IV). The first two groups were not handled, while the group 3 was manually restrained for 2 min for a mock injection of 0.2 ml saline into the ventral tail vein. Baseline HR was similar in all groups and handling caused a significant tachycardia ($p = 0.031$) in group three. When given IV to undisturbed animals, both propofol and alfaxalone induced a significant increase in HR ($p = 0.0022$ and $p = 0.0045$, respectively) lasting approximately 30 min, but with values only significantly exceeding baseline for the first 5 min for propofol and the first 10 min with alfaxalone. Handling caused a significant increase in MAP ($p = 0.0313$). Propofol did not affect MAP ($p = 0.1064$), while alfaxalone caused a marked hypertension (although only significant at 2 min; $p = 0.031$). Manual restraint significantly increases both HR and MAP, which may lead to a masking of true cardiovascular effects of anaesthetic agents.

1. Introduction

Propofol is used extensively for anaesthetic induction in reptiles and where available, alfaxalone is gaining similar popularity (Bertelsen, 2014; Schumacher and Mans, 2014). Intravenous injection with propofol provides rapid and effective anaesthetic induction in lizards (Bennett et al., 1998), snakes (Anderson et al., 1999), and chelonians (MacLean et al., 2008; Ziolo and Bertelsen, 2009). Similarly, intravenous, intramuscular or subcutaneous injection of alfaxalone provides anaesthetic induction in snakes (James et al., 2018), lizards (Bertelsen and Sauer, 2011; Doss et al., 2017), chelonians (Kischinovsky et al., 2013; Shepard et al., 2013; Knotek, 2014; Phillips et al., 2017) and crocodilians (Olsson et al., 2013).

The two drugs exert very similar clinical effects, but their cardiovascular effects in snakes are poorly studied. Knowledge of cardiopulmonary effects of anaesthetic agents is essential for safe management during anaesthesia, yet even basic data on heart rate (HR) and mean arterial blood pressure (MAP) is scarcely available for reptiles, and the validity of the limited available data may be hampered by the difficulties of obtaining correct baseline parameters prior to induction of anaesthesia.

Physical restraint of reptiles typically induces tachycardia and tachypnea (Stinner and Ely, 1993; Cabanac and Cabanac, 2000; Wang et al., 2001). This may lead to difficulty in interpreting data from anaesthetic trials, where animals are manually restrained, as the effects of restraint may obscure or exacerbate effects of the anaesthetics (e.g., Bertelsen and Sauer, 2011).

The objectives of this study were to 1) characterise the effect on MAP and HR of manual handling of snakes for anaesthetic induction, and 2) characterise and compare the development in MAP and HR during anaesthetic induction with propofol and alfaxalone.

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2. Materials and methods

2.1. Experimental animals

Twenty adult South American rattlesnakes (*Crotalus durissus*; 9 males and 11 females) were obtained from the Butantan institute in Sao Paulo and transported to Rio Claro where they were maintained in vivaria at natural temperatures and light regimes (daily amplitude of 25–30 °C; Light:Dark cycle of 12:12). Their mean body mass (±SEM) was 615 ± 42 g (range: 408–1067 g) and mean body length (snout-to-vent) was 98 ± 2.2 cm (range: 90–115 cm). The snakes were clinically healthy, as based on body condition, activity and a visual exam, and subsequent post-mortem examinations were unremarkable except for intestinal nematodiasis in some individuals. The snakes were fasted for 3 weeks prior to experiments to avoid postprandial changes in acid-base status and metabolism (Arvedsen et al., 2005). Standard precautions when housing and handing venomous snakes were taken, and all procedures were approved by the local Ethics Committee (Comissão de Ética no Uso de Animais) at University of São Paulo State (CEUA-UNESP).

2.2. Study design and experimental protocol

For catheterisation, snakes were manually restrained and anaesthetised with propofol (PropoVet Multidose, 10 mg/ml, Abbott Laboratories Ltd., Maidenhead, UK; 15 mg kg^{-1}) injected in the ventral tail vein. Following local analgesia with lidocaine subcutaneously immediately cranially to the heart, an incision was made to expose and occlusively catheterise the vertebral artery, after which the catheter was exteriorized and sutured into place (e.g., Skals et al., 2005). This procedure is commonly used in physiological research (e.g., Wang et al., 2001; de Andrade et al., 2004; Skals et al., 2005; Skovgaard et al., 2009). As the vertebral artery is occluded, and the catheter tip advanced to the opening into the right aorta, pressures measured are central, and substances injected are diluted massively, and are effectively central injections rather than arterial per se. Following recovery, snakes were transferred to a perforated transparent plastic container (35 × 25 × 10cm) and left in a quiet room until the following day. Room temperature was maintained at 26–28 °C.

Approximately 24 h following instrumentation, the arterial blood pressure was measured by connecting the arterial catheter to a Baxter Edward disposable pressure transducer (Baxter Edward model PX600; Irvine, CA, USA) positioned at heart level. The signal was amplified using an in-house-built preamplifier, and collected on a Biopac MP100 data acquisition system (Biopac System, Inc., Goleta, CA, USA) at 100 Hz. The transducer was calibrated daily against a static water column. HR was derived from the pulsatile pressure signal.

The snakes were kept individually in plastic containers that were covered by cloth and placed in a separate room to alleviate disturbance from the investigators, and all resting (baseline) values for HR and MAP could be recorded without disturbing the snakes. Blood pressure and HR were recorded for a period of 15–30 min, and each snake was then randomly assigned to one of three groups: the first two groups were not restrained or handled in any way. Group 1 ($n = 7$) received alfaxalone (Alfaxan®, Jurox Ltd., Malvern Link, UK; 15 mg kg^{-1}) through the indwelling catheter, Group 2 ($n = 6$) received propofol (15 mg kg^{-1}) through the catheter. To mimic routine IV administration, Group 3 ($n = 6$) was manually restrained for 2 min for a mock injection of 0.2 ml saline into the ventral tail vein. Simultaneously, propofol (15 mg kg^{-1}), was injected into the indwelling catheter as in the two other experimental groups. Catheters were immediately flushed with saline, and blood pressure was measured continuously over the next 30 min. The dosages were based on pilot studies in the species. Following full recovery form anaesthesia, all snakes were euthanized with pentobarbital IV, and subjected to necropsy.

2.3. Data analysis

From the blood pressure trace, representative values over consecutive periods of 30–90 s for analysis were obtained at baseline prior to induction, during handling (if applicable), and at 2, 5, 10, 20 and 30 min following injection. The normality of the data was difficult to assess due to the small group sizes, so non-parametric tests were chosen for conservativity. The effect of handling was assessed using a Wilcoxon matched-pairs signed rank test using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA). Changes over time were assessed for each group using a Friedman's test followed by Dunn's multiple comparisons test. $p < 0.05$ was considered significant, and all data are expressed as mean ± 1 SEM.

3. Results

Baseline HR was similar in all groups 26.5 ± 2 min^{-1}, and handling significantly increased the frequency (median of difference 20.75; $p = 0.031$). Both propofol and alfaxalone induced a significant increase in HR in the undisturbed animals ($p = 0.0022$ and $p = 0.0045$, respectively) lasting approximately 30 min, but with values only significantly exceeding baseline for the first 5 min for propofol and the first 10 min with alfaxalone (Fig. 1). Baseline blood pressure was 42.2 ± 1.7 mmHg for all groups, and handling caused a significant increase in MAP (median of difference 27.65; $p = 0.0313$). In the undisturbed animals, propofol had no measurable effect on MAP ($p = 0.1064$), while alfaxalone caused a marked increase in MAP (although only significant at 2 min, $p = 0.031$) (Fig. 1; Table 1).

4. Discussion

Handling and restraint caused marked increases in both HR and MAP of the rattlesnakes. This was not unexpected, but has largely been ignored in anaesthesia research, mainly due to the difficulty of obtaining resting values without indwelling monitoring equipment as used in this study. Both propofol and alfaxalone resulted in a marked increase in HR in the undisturbed rattlesnakes, which is congruent to the responses described in dogs and cats (Muir et al., 2008, 2009; Suarez et al., 2012; Maney et al., 2013), but in complete contrast to the stable level or decrease in HR previously reported in reptiles (Bennett et al., 1998; Ziolo and Bertelsen, 2009; Bertelsen and Sauer, 2011; Kischinovsky et al., 2013; Hansen and Bertelsen, 2013; Olsson et al., 2013). In all of these cases, the reason probably is that the "baseline" values for HR were to high as a consequence of the manual restraint needed to administer the anaesthetics. Of course, the clinical reality for reptiles will inevitably involve manual restraint to allow administration of these drugs, however, an understanding of the physiological consequences of both restraint and anaesthesia is important for safe anaesthesia and meaningful anaesthetic monitoring.

Consistently higher MAP was documented with alfaxalone than with propofol. In both dogs and cats, alfaxalone leads to hypotension and a reflex tachycardia (Muir et al., 2008, 2009). Reptiles, including rattlesnakes, are also endowed with baroreceptor reflexes (Lillywhite and Donald, 1994; Galli et al., 2005a, 2005b; Hernandez et al., 2011). The disassociation between HR and MAP in the anaesthetised rattlesnakes evident with both drugs in this study suggests that the normal baroreceptor reflex was suppressed by anaesthesia.

To obtain clean data for blood pressure and HR, no attempts were made to monitor or assist ventilation. Nevertheless, both drugs are commonly associated with apnoea, particularly when given intravenously (Bertelsen, 2014; Schumacher and Mans, 2014), and whilst all snakes recovered uneventfully, the authors recommend mechanical ventilation of anaesthetized snakes in apparent apnoea (Bertelsen et al., 2015; Jakobsen et al., 2017).

The dosages used were chosen based on a pilot study where they provided similar depth of anaesthesia in rattlesnakes, but were slightly

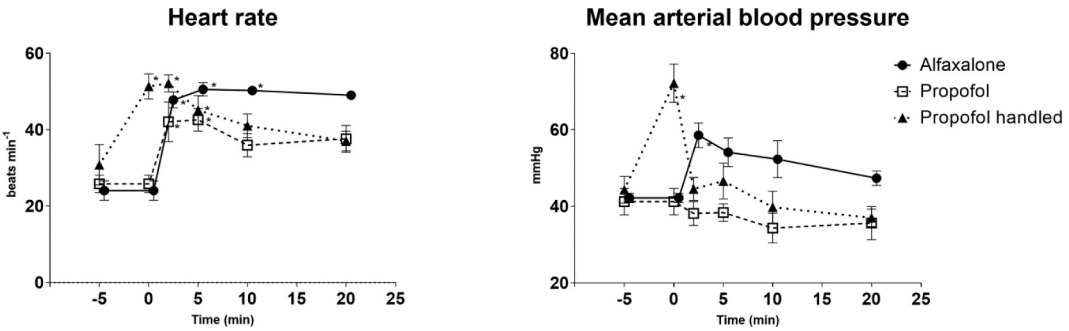

Fig. 1. Heart rate and mean arterial blood pressure of rattlesnakes induced at time 0 with either alfaxalone (15 mg kg^{-1}; circles) or propofol (15 mg kg^{-1}; squares) without handling or with propofol (15 mg kg^{-1}; triangles) injected during manual restraint. Time − 5 is baseline in undisturbed animals. All data are presented as mean ± 1 SEM, and values that significantly different from baseline are denoted by an asterisk (*).

Table 1
Heart rate and mean arterial blood pressure of rattlesnakes induced at time 0 with either alfaxalone (15 mg kg^{-1}) or propofol (15 mg kg^{-1}) without handling or with propofol (15 mg kg^{-1}) injected during manual restraint at time 0.

Time	Alfaxalone undisturbed		Propofol undisturbed		Propofol handled	
	MAP mmHg	HR bpm	MAP mmHg	HR bpm	mmHg	HR bpm
Baseline	41 ± 1.2	23 ± 2.6	41 ± 3.5	26 ± 2.3	44 ± 3.5	31 ± 5.3
0 min	–	–	–	–	72 ± 5*	51 ± 3.3*
2 min	58 ± 3.2*	47 ± 2.1*	38 ± 3.1	42 ± 5.2*	45 ± 3	52 ± 2.3*
5 min	53 ± 3.7	50 ± 1.7*	38 ± 2.3	43 ± 2.9*	47 ± 4.7	45 ± 3.8*
10 min	51 ± 4.8	49 ± 1.1*	34 ± 3.9	36 ± 3	40 ± 4.2	41 ± 3.1
20 min	46 ± 1.9	48 ± 0.8	36 ± 4.3	38 ± 3.5	37 ± 2.3	37 ± 2.6

Baseline represents values in undisturbed animals at time (around 5 min prior to injection or handling). All data are presented as mean ± 1 SEM, and values that significantly different from baseline are denoted by an asterisk (*).

higher than usual recommendations (Bertelsen, 2014; Knotek, 2014). Although anaesthetic depth and recovery times were not monitored in this study to minimize disturbance to the animals, snakes appeared to recover marginally faster from propofol suggesting that the alfaxalone could have been reduced slightly to obtain equipotency. Nonetheless, the cardiovascular effects should be representative for the two agents.

Anaesthetics and other veterinary drugs are often delivered by intravenous injection, while our approach to measure blood pressures and to administer pharmacological agents through the same arterial catheter is common in the field of comparative physiology (e.g., Lillywhite and Lillywhite and Seymour, 1978; de Andrade et al., 2004; Seebacher and Franklin, 2004). Given that the catheter tip was placed in the right aorta, the drugs were likely to be diluted in a similar manner as when injected in large central veins, and the drugs are likely to have reached the tissues in a similar time. Thus, we do not believe the pharmacodynamics were significantly affected, and we did not observe any adverse effects of arterial injections in any of the snakes. We were not able to assess long-term effects of occlusive cannulation of the vertebral artery as the snakes were euthanized less than 48 h after surgery.

There are only few reports on the influence of other anaesthetics on blood pressure in reptiles, and no previous studies on rattlesnakes. As would be expected from studies in mammals, isoflurane was reported to cause hypotension in iguanas (Mosley et al., 2004; Chinnadurai et al., 2010) as was sevoflurane in desert tortoises (Rooney et al., 1999), although baseline values may have been affected by handling. Ketamine alone caused MAP to rise in corn snakes (Schumacher et al., 1997), and medetomidine-ketamine increased MAP in gopher tortoises (Dennis and Heard, 2002). Interestingly, decreased MAP was described following medetomidine administration in desert tortoises (Sleeman and Gaynor, 2000).

The results presented suggest that propofol is less physiologically disruptive than alfaxalone, and further studies should explore the pharmacodynamics of alfaxalone administered intramuscularly or subcutaneously as is often practiced clinically.

In conclusion, manual restraint causes pronounced hypertension and tachycardia of snakes, and the magnitude of these effects may mask the true cardiovascular effects of the anaesthetic drugs when compared to "baseline". When administered through indwelling catheters to undisturbed rattlesnakes, both propofol and alfaxalone causes significant increases in HR, and alfaxalone leads to a transient rise in blood pressure.

Author contributions

All authors contributed to study design, logistics and data collection. MFB and TW analysed the data and prepared the manuscript that was approved by all authors.

Declaration of Competing Interest

We declare no conflicts of interest.

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